UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/996,484	11/28/2001	Yen Choo	8325-2004 G8-US1	2713

20855 7590 06/04/2008

ROBINS & PASTERNAK
1731 EMBARCADERO ROAD
SUITE 230
PALO ALTO, CA 94303

EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	PAPER NUMBER
1636	
MAIL DATE	DELIVERY MODE
06/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/996,484	CHOO ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,7,8,10,11,13-15,21-26,31,34,35 and 38-48* is/are pending in the application.

4a) Of the above claim(s) *1,2,4,5,7,8,10,11,13-15,21-26,31,35 and 38-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a reply to the Paper filed 4 March 2008 in response to the Non-Final Office Action mailed 14 December 2007. Claims 1, 2, 4, 5, 7, 8, 10, 11, 13-15, 21-26, 31, 35 and 38-47 have been withdrawn from consideration and claims 34 and 48 were considered in the 14 December Office action. Claims 1, 34, and 48 were amended in the 4 March Paper. Claims 1, 2, 4, 5, 7, 8, 10, 11, 13-15, 21-26, 31, 34, 35 and 38-48 are pending and claims 34 and 48 are under consideration.

Response to Amendment and Arguments

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Rejection of claims 34 and 48 under 35 U.S.C. 102(b) as being anticipated by Gilman et al. WO 96/06110 is **withdrawn** in view of the amendment of the claims to recite that the claims to recite that the first or second polypeptide comprises a "non-naturally occurring Cys2-His2 zinc finger binding domain." Gilman et al. does not teach that the zinc finger binding domain described therein must be non-naturally occurring.

New Grounds Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34 and 48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The claims of the instant case are directed to a complex comprising a first or second polypeptide delimited as comprising a "non-naturally occurring Cys2-His2 zinc finger binding domain". The specification states, "The term 'a non-naturally occurring binding domain' means that the binding domain does not occur in nature, even as a part of a larger molecule" (page 3, lines 29-31). Thus, the zinc finger binding domain of the claims embraces a genus of all such domains that do not occur in nature. Therefore, possession of the claimed genus requires that, at the time the application was filed, the skilled artisan would have been able to distinguish zinc finger DNA binding domains that do not occur in nature (i.e., the claimed invention) from zinc

finger DNA binding domains that do occur in nature. However, proteins in nature are polymorphic as a consequence of continual mutation and the full scope of zinc finger domains occurring in nature (i.e., all naturally occurring variants in all species) is unknown. Even if a zinc finger domain is subject to deliberate mutagenesis in the laboratory, it is impossible to know if the mutagenized zinc finger domain is "non-naturally occurring" and therefore within the scope of the claim limitation without knowing the full scope of zinc finger domains that do occur in nature. As the instant application fails to describe the relevant identifying characteristics of a zinc finger DNA binding domain that does not occur in nature such that one of ordinary skill in the art would be able to distinguish zinc finger DNA binding domains that occur in nature from zinc finger DNA binding domains that do not occur in nature, the skilled artisan would conclude that applicant was not in possession of the full scope of the claimed genus at the time of filing.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 34 and 48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite in reciting that a polypeptide comprises a "non-naturally occurring Cys2-His2 zinc finger binding domain". The specification states, "The term 'a non-naturally occurring binding domain' means that the binding domain does not occur in nature, even as a part of a larger molecule" (page 3, lines 29-31). Thus, the claim limitation requires that zinc finger binding domain does not occur in nature. However, proteins in nature are

polymorphic as a consequence of continual mutation and the full scope of zinc finger domains occurring in nature is unknown. Even if a zinc finger domain is subject to deliberate mutagenesis in the laboratory, the skilled artisan would not know if the mutagenized zinc finger domain is "non-naturally occurring" and therefore within the scope of the claim limitation, because the scope of zinc finger domains occurring in nature is unknown. In other words, the scope of the claim limitation is indefinite because the benchmark used to determine whether any given zinc finger domain is "non-naturally occurring" is unknown and unknowable.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 34 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gilman et al. WO 96/06110 (previously made of record).

Claim 34 is directed to a complex comprising a heterodimer comprising a first and second polypeptide, wherein the first and second polypeptides bind to DNA and the first or second polypeptide comprises an engineered, non-naturally occurring Cys2-His2 zinc finger binding domain, and a ligand that binds to the first and second polypeptides and mediates heterodimerization of the first and second polypeptides.

Claim 48 is directed to a switching system comprising a first and second polypeptide and a ligand in which the first polypeptide binds to the second polypeptide to form a heterodimer and the binding of the first and second polypeptides is mediated by binding the ligand to the first and second polypeptides, wherein the first and second polypeptides bind to DNA and the first or second polypeptide comprises an engineered Cys2-His2 zinc finger DNA binding domain.

Gilman et al. teaches composite DNA-binding proteins in which two or more heterologous DNA-binding domains are linked together through an association mediated by a multimerizing agent. (See, e.g., page 2, lines 9-13; page 3, lines 1-6; and page 8, lines 9-19.) Gilman et al. teaches that the multimerizer-linked composite DNA-binding proteins comprise two or more chimeric proteins, each comprising at least one binding site for a multimerizing ligand and at least one component DNA-binding domain. (See especially the first full paragraph on page 5.) Thus, Gilman et al. teaches a complex or switching system comprising first and second proteins and a ligand (i.e., multimerizing agent), wherein the ligand binds to both the first and second polypeptides such that the first and second polypeptides are joined to form a heterodimer (i.e., the polypeptides comprise, at least, heterologous DNA binding domains).

Gilman et al. further teaches Cys2-His2 zinc finger DNA binding domains as one of a small number of explicitly named classes of DNA binding domains that might be comprised by

the composite DNA-binding proteins. In addition, Gilman et al. teaches that the zinc finger DNA-binding domains can be engineered by mutagenesis to provide a DNA-binding domain having decreased, increased or altered recognition specificity of DNA binding. (See especially the first full paragraph on page 10.)

Although Gilman et al. does not explicitly teach that the engineered Cys2-His-2 zinc finger binding domain should not occur in nature and, as described above, it would be impossible to know whether any given engineered binding domain occurs in nature, Gilman et al. does teach that the engineered DNA binding domains might be selected from phage display libraries (see especially page 10, lines 13-15), which would comprise large numbers of random mutants. As it is reasonable to expect that at least some of the DNA binding domains selected in that manner would be non-naturally occurring, the inclusion of a non-naturally occurring engineered Cys2-His-2 zinc finger binding domain in the complex of Gilman et al. would have been obvious to one of ordinary skill in the art at the time the invention was made because one would be motivated to use any DNA binding domain having increased affinity or altered specificity as contemplated by Gilman et al. Absent evidence to the contrary one would have a reasonable expectation of success in obtaining a non-naturally occurring engineered Cys2-His2 zinc finger binding domain by the method of phage display because it is routine in the art to isolate peptides having desirable properties, such as altered DNA binding affinity or specificity, by the process of phage display.

In view of the foregoing, the complex and switching system of the instant claims 34 and 48, as a whole, would have been obvious to one of ordinary skill in the art at the time the

invention was made. Therefore, the claims are properly rejected under 35 USC § 103(a) as obvious over the art.

Response to Arguments

In response to the previous rejection of the claims as anticipated by Gilman et al. Applicant contends that Gilman uses only naturally occurring Cys2-His2 zinc fingers in their composite proteins. This argument is not persuasive with respect to the obviousness rejection set forth herein because, as stated in the previous Office Action (page 5), "Gilman et al. teaches that the zinc finger DNA-binding domains can be engineered by mutagenesis to provide a DNA-binding domain having decreased, increased or altered recognition specificity of DNA binding. (See especially the first full paragraph on page 10.)" and, for the reasons set forth herein, it would have been obvious to one of ordinary skill in the art at the time of invention to select any engineered Cys2-His2 zinc finger binding domain having the properties identified by Gilman et al. as desirable, including those that are non-naturally occurring.

Applicant further contends that Gilman fails to teach or suggest heterodimers of two zinc finger domains in which dimerization of the two zinc finger (ZF) domains is mediated by a ligand. Rather, as set forth on page 9 of Gilman, the reference clearly indicates that when a single linker is used between two DNA-binding domains, one of the DNA-binding domains is a homeodomain.

This argument is not persuasive. The instant claims recite, "wherein the first or second polypeptide comprises an engineered, non-naturally occurring Cys2-His2 zinc finger binding domain." The claims require only that one of the two polypeptides of the complex or switching

system comprises a non-naturally occurring Cys2-His2 zinc finger binding domain. Therefore, the complexes comprising a zinc finger and a homeodomain contemplated on pages 9-10 of Gilman et al. read on the claimed invention.

Furthermore, even if the claims had required that both proteins of the complex comprise a Cys2-His2 zinc finger binding domain, the structures HD—L—ZF and ZF—L—HD set forth on page 9 are merely examples of possible configurations and there is no teaching in Gilman et al. to indicate that the complex must comprise at least a homeodomain. In addition, at page 5, lines 1-5, Gilman et al. teaches the generic structure DBD1—L—DBD2 and in the paragraph bridging pages 9-10 Gilman et al. teaches that when structured so that the linker (L) is a multimerizing ligand "each chimeric protein contains only a subset or portion of one of the forgoing composite DBDs..." In view of these teachings, any configuration of the generic DBD1—L—DBD2 structure would have been obvious to one of ordinary skill in the art at the time the invention was made.

Applicant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claims stand rejected under 35 USC § 103(a) as obvious over the art.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M. Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D. can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) (http://pair-

direct.uspto.gov) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Daniel M Sullivan/
Primary Examiner, Art Unit 1636